

# Pupillary Reflex Dilation to Predict Movement

## *A Step Forward Toward Real-time Individualized Intravenous Anesthetics*

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**S**URGEONS often ask if the patient is ready for the case to begin. An affirmative answer might require an awkward retraction if the patient then moves or coughs. When using total intravenous anesthesia (TIVA), we are never truly certain how to answer the surgeon's query, unless the patients are paralyzed. By contrast, with volatile anesthetics, we can confidently answer that the patient will not remember or move based on the limited inter-individual variability in the concentration–effect relationships.<sup>1</sup> In this issue of *ANESTHESIOLOGY*, Guglielminotti *et al.*<sup>2</sup> have proposed a simple pupillary test that might provide the anesthesia provider with a more precise answer for TIVA. These authors suggest that depression of pupillary reflex dilation in response to a standardized noxious stimulus will predict nonmovement to a surgical stimulus. The pupillary test predicted nonmovement with an accuracy that was equivalent to pharmacokinetic–pharmacodynamic (PK/PD) model predictions for propofol–remifentanyl anesthetics in healthy young females.

There are similarities between the movement reflex and reflex dilation of the pupil during anesthesia. Both reflexes are subcortically mediated, initiated by nociceptors, and suppressed by opioids.<sup>3</sup> Opioids are known to essentially obliterate pupillary reflex dilation at concentrations equivalent to 5 ng/ml of remifentanyl in the presence of propofol.<sup>2</sup> As reported by these authors, failure of pupillary reflex dilation essentially guaranteed absence of movement to a surgical stimulus.



***“Patients have widely differing responses to opioids, and this technique might allow us to deliver these drugs during general anesthesia in a more precise fashion.”***

Intermittent testing of patient responsiveness with a standardized noxious stimulus during anesthesia is an idea that has been slow to develop, but is overdue because it has the potential to add precision to the management of our TIVA<sup>2</sup> and combined regional–general anesthetics.<sup>4,5</sup> If we decide to use intermittent testing to detect nociception, then it becomes important to know how to provide the stimulus and what parameters to measure after the stimulus.

The stimulus parameters of the “standardized noxious test” are slightly different for each reference cited by Guglielminotti *et al.*,<sup>2</sup> so the stimulus is only standardized for each specific study. Some of the factors that can affect the response to the stimulus include the intensity of the stimulating current, the type of stimulating electrodes, the duration of the stimulus, and the frequency of the stimulus train. There is a trend toward the use of skin surface electrocardiographic electrodes, 60 mA current intensity, and 100 Hz frequency of stimulation, and Guglielminotti *et al.*<sup>2</sup> used these stimulating parameters. If placed over the ulnar nerve, the same stimulator might be used to evaluate the neuromuscular junction.

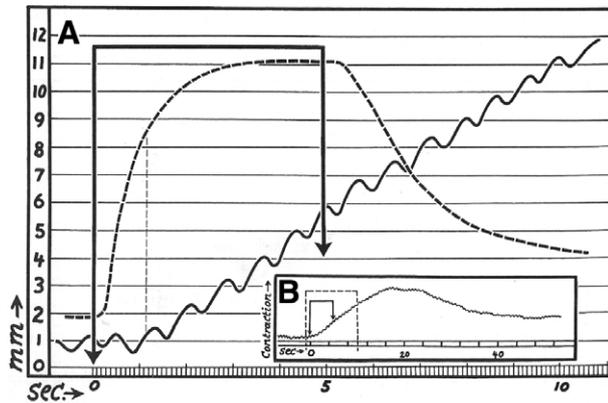
The responses to measure after the stimulus also differ. Despite the fact that it has been known for over 50 yr that the sympathetic nervous system is relatively slow to respond during anesthesia compared to reflex dilation of the pupil (fig. 1), hemodynamic changes in response to nociception are a common parameter used to titrate hypnotics and opioids.

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**Fig. 1.** (A) Reflex dilation of the feline pupil during pentobarbital anesthesia is abrupt compared to the vasoconstrictor response to the same noxious stimulus (5 s hypothalamic stimulus delivered between the arrows). The dashed line shows the pupillary dilation, and the solid line is vessel caliber through the ear auricle on the same side (vasoconstriction is “up” in arbitrary units). Note that the pupil has dilated almost completely during the latent phase of the vascular response. (B) The vascular response is shown on a different time scale. The peak vascular response occurred at about 20 s after the application of the noxious stimulation, and the effect was still present 1 min after the stimulus was removed.<sup>6</sup> Reproduced, with permission, from Loewenfeld, *Doc Ophthalmol* 1958; 12:184–448.

Activation of the electroencephalogram is also often used to detect nociception, but it is also a sluggish and inconsistent response.<sup>7</sup> A nociceptive response such as pupillary reflex dilation that develops within a few seconds is an advantage over a response that takes 20 to 30 s because other factors involved in the management of the case can confound sluggish and delayed responses. Other advantages of pupillary reflex dilation are that it is not depressed by  $\beta$ -adrenergic blocking agents<sup>8</sup> or muscle relaxants.<sup>9</sup>

Although pupillary reflex dilation is a useful parameter to measure in this context, there are disadvantages. The measurement requires intermittent access to the eye and the cornea is briefly exposed. The oculomotor nerve that innervates the pupillary sphincter is dysfunctional in certain disease states, and there are rare syndromes such as senile miosis, Adie syndrome, prior eye surgery, and diabetic neuropathy, in which the pupil is relatively immobile. Although these syndromes are rare, they would confound the use of pupillary reflex dilation as a measure of nociception. One method to screen for the immobile pupil is to examine the pupillary light reflex with infrared pupillometry before anesthesia. The light reflex and pupillary reflex dilation during anesthesia are both mediated by the parasympathetic division of the autonomic nervous system. A normal light reflex<sup>10</sup> essentially rules out issues with tonic or sluggish pupillary responses.

Guglielminotti *et al.*<sup>2</sup> were unable to show any advantage of using the pupillary reflex dilation over the predictions made by PK/PD models for propofol–remifentanyl anesthetics in their experimental population of healthy women. However, PK/PD models of TIVA are limited

because they are developed in healthy surgical patients who demonstrate stationary physiologic conditions.<sup>1</sup> The predictive ability of PK/PD models has not been tested in other physiologic conditions. In common clinical situations where there are alterations in cardiac output or its distribution, such as obesity, hemorrhage, pneumoperitoneum, or extremes of age, these PK/PD models may perform poorly.<sup>11</sup> One might expect that the pupillary measurement would outperform the targeted infusions as a predictor of nonmovement in situations where PK/PD model predictions might be inaccurate. The relative advantage of using reflex dilation compared to targeted infusions as predictors of nonmovement in these common subgroups will require additional studies.

The authors targeted the propofol concentration in these healthy volunteers to 4 ng/ml and then used varying concentrations of remifentanyl to provide additional analgesia. However, propofol given with nitrous oxide without opioids does not block pupillary reflex dilation even though the subjects do not move in response to the same stimulus.<sup>7</sup> Guglielminotti *et al.*<sup>2</sup> recognize that they are essentially evaluating the effect of remifentanyl on movement and that the use of pupillary reflex dilation to predict nonmovement might vary at different targeted propofol concentrations. In addition, other IV adjuvants such as ketamine, dexmedetomidine,<sup>12</sup> and lidocaine<sup>13</sup> might alter the relationship between pupillary reflex dilation and movement.

In spite of these issues, the observations of Guglielminotti *et al.*<sup>2</sup> are valuable and add insight to how we might succeed in determining the opposing factors of nociception and antinociception during surgical anesthesia. Patients have widely differing responses to opioids, and this technique might allow us to deliver these drugs during general anesthesia in a more precise fashion. Meanwhile, we look forward to additional studies examining this pupillary test to predict nonmovement in a more diverse population.

## Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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